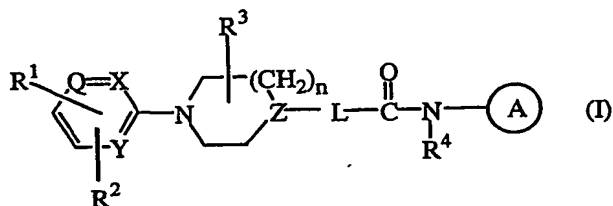


Claims

1. A compound of formula (I),



the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

10 n is 0, 1, 2 or 3 and when n is 0 then a direct bond is intended;

each Q is nitrogen or $\text{—C}\equiv$;

each X is nitrogen or $\text{—C}\equiv$;

each Y is nitrogen or $\text{—C}\equiv$;

each Z is nitrogen or $\text{—CH}\equiv$;

20 R^1 is —C(O)NR^7R^8 , —N(H)C(O)R^9 , $\text{—C(O)—C}_{1-6}\text{alkanediylSR}^9$, $\text{—NR}^{10}\text{C(O)N(OH)R}^9$, $\text{—NR}^{10}\text{C(O)C}_{1-6}\text{alkanediylSR}^9$, $\text{—NR}^{10}\text{C(O)C=N(OH)R}^9$ or another Zn-chelating-group

wherein R^7 and R^8 are each independently selected from hydrogen, hydroxy, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl or aminoaryl;

25 R^9 is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, aryl C_{1-6} alkyl, C_{1-6} alkylpyrazinyl, pyridinone, pyrrolidinone or methylimidazolyl;
 R^{10} is independently selected from hydrogen or C_{1-6} alkyl;

30 R^2 is hydrogen, halo, hydroxy, amino, nitro, C_{1-6} alkyl, C_{1-6} alkyloxy, trifluoromethyl, di(C_{1-6} alkyl)amino, hydroxyamino or naphthalenylsulfonylpyrazinyl;

35 R^3 is hydrogen, hydroxy, amino, hydroxy C_{1-6} alkyl, C_{1-6} alkyl, C_{1-6} alkyloxy, aryl C_{1-6} alkyl, aminocarbonyl, hydroxycarbonyl, amino C_{1-6} alkyl, aminocarbonyl C_{1-6} alkyl, hydroxycarbonyl C_{1-6} alkyl, hydroxyaminocarbonyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylamino C_{1-6} alkyl or di(C_{1-6} alkyl)amino C_{1-6} alkyl;

when Z is equal to nitrogen, then -L- is a direct bond;

when Z is equal to $-\text{CH}-$, then -L- is -NH- or the bivalent radical

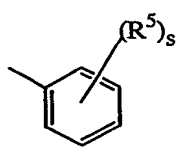
$-\text{C}_{1-6}\text{alkanediylnH}-$;

5

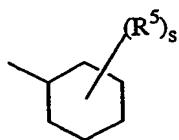
R^4 is hydrogen, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{3-10}\text{cycloalkyl}$, hydroxy $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{1-6}\text{alkyloxyC}_{1-6}\text{alkyl}$, di($\text{C}_{1-6}\text{alkyl}$)amino $\text{C}_{1-6}\text{alkyl}$ or aryl;

 is a radical selected from

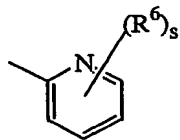
10



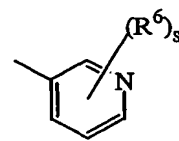
(a-1)



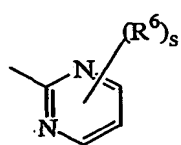
(a-2)



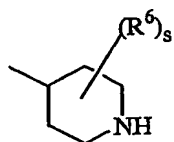
(a-3)



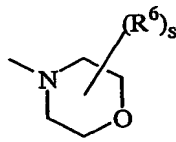
(a-4)



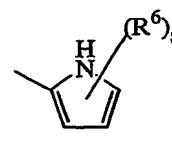
(a-5)



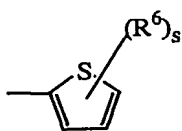
(a-6)



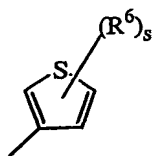
(a-7)



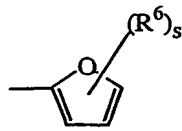
(a-8)



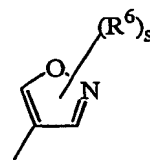
(a-9)



(a-10)

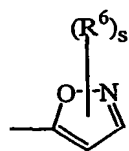


(a-11)

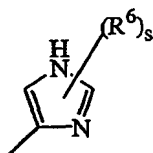


(a-12)

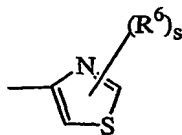
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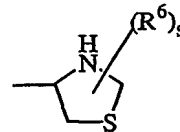
(a-13)



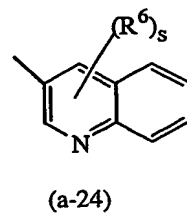
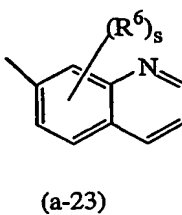
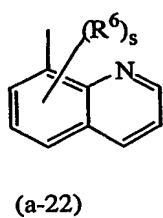
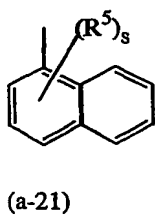
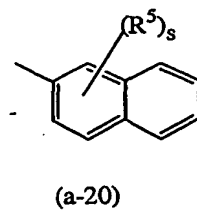
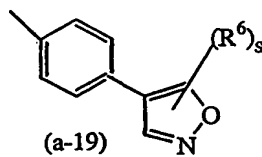
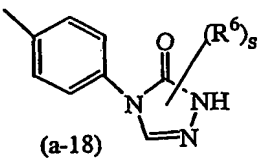
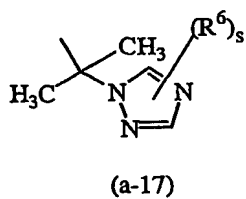
(a-14)



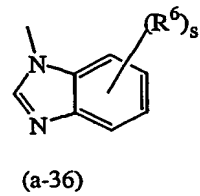
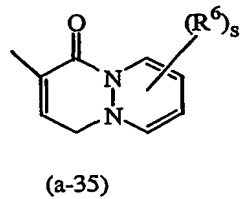
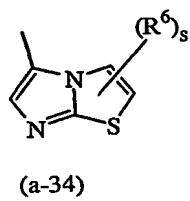
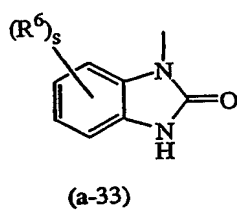
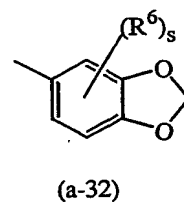
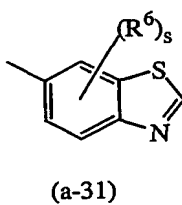
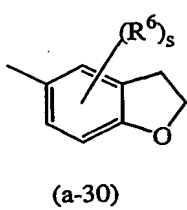
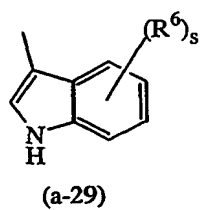
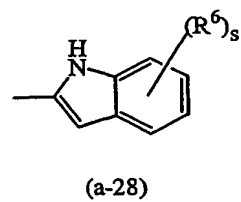
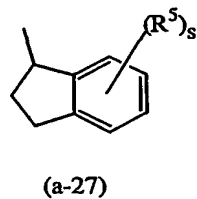
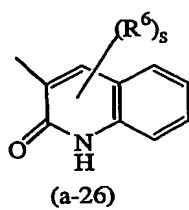
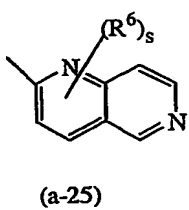
(a-15)



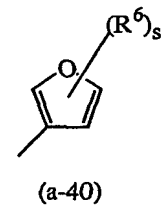
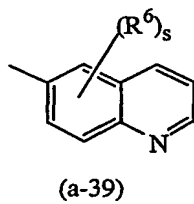
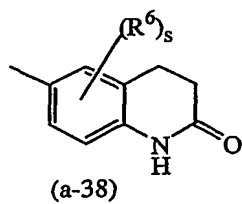
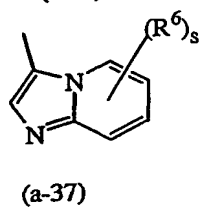
(a-16)

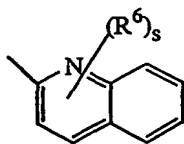


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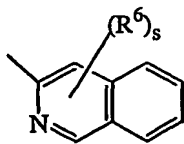


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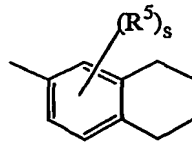




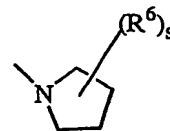
(a-41)



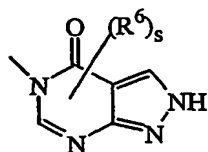
(a-42)



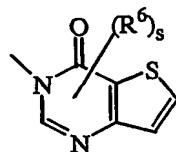
(a-43)



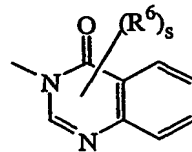
(a-44)



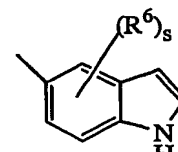
(a-45)



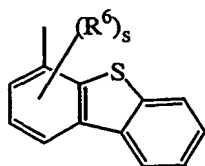
(a-46)



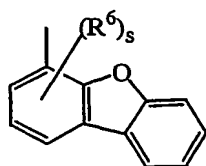
(a-47)



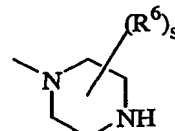
(a-48)



(a-49)



(a-50)



(a-51)

5

wherein each s is independently 0, 1, 2, 3, 4 or 5;

each R^5 and R^6 are independently selected from hydrogen; halo; hydroxy; amino; nitro;

trihaloC₁₋₆alkyl; trihaloC₁₋₆alkyloxy; C₁₋₆alkyl; C₁₋₆alkyl substituted with aryl and

C₃₋₁₀cycloalkyl; C₁₋₆alkyloxy; C₁₋₆alkyloxyC₁₋₆alkyloxy; C₁₋₆alkylcarbonyl;

10

C₁₋₆alkyloxycarbonyl; C₁₋₆alkylsulfonyl; cyanoC₁₋₆alkyl; hydroxyC₁₋₆alkyl;

hydroxyC₁₋₆alkyloxy; hydroxyC₁₋₆alkylamino; aminoC₁₋₆alkyloxy;

di(C₁₋₆alkyl)aminocarbonyl; di(hydroxyC₁₋₆alkyl)amino; (aryl)(C₁₋₆alkyl)amino;

di(C₁₋₆alkyl)aminoC₁₋₆alkyloxy; di(C₁₋₆alkyl)aminoC₁₋₆alkylamino;

di(C₁₋₆alkyl)aminoC₁₋₆alkylaminoC₁₋₆alkyl; arylsulfonyl; arylsulfonylamino;

15

aryloxy; aryloxyC₁₋₆alkyl; arylC₂₋₆alkenediyl; di(C₁₋₆alkyl)amino;

di(C₁₋₆alkyl)aminoC₁₋₆alkyl; di(C₁₋₆alkyl)amino(C₁₋₆alkyl)amino;

di(C₁₋₆alkyl)amino(C₁₋₆alkyl)aminoC₁₋₆alkyl;

di(C₁₋₆alkyl)aminoC₁₋₆alkyl(C₁₋₆alkyl)amino;

di(C₁₋₆alkyl)aminoC₁₋₆alkyl(C₁₋₆alkyl)aminoC₁₋₆alkyl;

20

aminosulfonylamino(C₁₋₆alkyl)amino;

aminosulfonylamino(C₁₋₆alkyl)aminoC₁₋₆alkyl;

di(C₁₋₆alkyl)aminosulfonylamino(C₁₋₆alkyl)amino;

di(C₁₋₆alkyl)aminosulfonylamino(C₁₋₆alkyl)aminoC₁₋₆alkyl; cyano; thiophenyl;

thiophenyl substituted with di(C₁₋₆alkyl)aminoC₁₋₆alkyl(C₁₋₆alkyl)aminoC₁₋₆alkyl;

25

di(C₁₋₆alkyl)aminoC₁₋₆alkyl, C₁₋₆alkylpiperazinylC₁₋₆alkyl,

hydroxyC₁₋₆alkylpiperazinylC₁₋₆alkyl,

hydroxyC₁₋₆alkyloxyC₁₋₆alkylpiperazinylC₁₋₆alkyl,

di(C₁₋₆alkyl)aminosulfonylpiperazinylC₁₋₆alkyl,
 C₁₋₆alkyloxypiperidinyl, C₁₋₆alkyloxypiperidinylC₁₋₆alkyl, morpholinylC₁₋₆alkyl,
 hydroxyC₁₋₆alkyl(C₁₋₆alkyl)aminoC₁₋₆alkyl, or di(hydroxyC₁₋₆alkyl)aminoC₁₋₆alkyl;
 furanyl; furanyl substituted with hydroxyC₁₋₆alkyl; benzofuranyl; imidazolyl;
 5 oxazolyl; oxazolyl substituted with aryl and C₁₋₆alkyl; C₁₋₆alkyltriazolyl; tetrazolyl;
 pyrrolidinyl; pyrrolyl; piperidinylC₁₋₆alkyloxy; morpholinyl; C₁₋₆alkylmorpholinyl;
 morpholinylC₁₋₆alkyloxy;
 morpholinylC₁₋₆alkyl; morpholinylC₁₋₆alkylamino;
 morpholinylC₁₋₆alkylaminoC₁₋₆alkyl; piperazinyl; C₁₋₆alkylpiperazinyl;
 10 C₁₋₆alkylpiperazinylC₁₋₆alkyloxy; piperazinylC₁₋₆alkyl;
 naphtalenylsulfonylpiperazinyl; naphtalenylsulfonylpiperidinyl; naphtalenylsulfonyl;
 C₁₋₆alkylpiperazinylC₁₋₆alkyl; C₁₋₆alkylpiperazinylC₁₋₆alkylamino;
 C₁₋₆alkylpiperazinylC₁₋₆alkylaminoC₁₋₆alkyl; C₁₋₆alkylpiperazinylsulfonyl;
 aminosulfonylpiperazinylC₁₋₆alkyloxy; aminosulfonylpiperazinyl;
 15 aminosulfonylpiperazinylC₁₋₆alkyl; di(C₁₋₆alkyl)aminosulfonylpiperazinyl;
 di(C₁₋₆alkyl)aminosulfonylpiperazinylC₁₋₆alkyl; hydroxyC₁₋₆alkylpiperazinyl;
 hydroxyC₁₋₆alkylpiperazinylC₁₋₆alkyl; C₁₋₆alkyloxypiperidinyl;
 C₁₋₆alkyloxypiperidinylC₁₋₆alkyl; piperidinylaminoC₁₋₆alkylamino;
 piperidinylaminoC₁₋₆alkylaminoC₁₋₆alkyl;
 20 (C₁₋₆alkylpiperidinyl)(hydroxyC₁₋₆alkyl)aminoC₁₋₆alkylamino;
 (C₁₋₆alkylpiperidinyl)(hydroxyC₁₋₆alkyl)aminoC₁₋₆alkylaminoC₁₋₆alkyl;
 hydroxyC₁₋₆alkyloxyC₁₋₆alkylpiperazinyl;
 hydroxyC₁₋₆alkyloxyC₁₋₆alkylpiperazinylC₁₋₆alkyl;
 (hydroxyC₁₋₆alkyl)(C₁₋₆alkyl)amino; (hydroxyC₁₋₆alkyl)(C₁₋₆alkyl)aminoC₁₋₆alkyl;
 25 hydroxyC₁₋₆alkylaminoC₁₋₆alkyl; di(hydroxyC₁₋₆alkyl)aminoC₁₋₆alkyl;
 pyrrolidinylC₁₋₆alkyl; pyrrolidinylC₁₋₆alkyloxy; pyrazolyl; thiopyrazolyl; pyrazolyl
 substituted with two substituents selected from C₁₋₆alkyl or trihaloC₁₋₆alkyl;
 pyridinyl; pyridinyl substituted with C₁₋₆alkyloxy, aryloxy or aryl; pyrimidinyl;
 tetrahydropyrimidinylpiperazinyl; tetrahydropyrimidinylpiperazinylC₁₋₆alkyl;
 30 quinolinyl; indolyl; phenyl; phenyl substituted with one, two or three substituents
 independently selected from halo, amino, nitro, C₁₋₆alkyl, C₁₋₆alkyloxy,
 hydroxyC₁₋₄alkyl, trifluoromethyl, trifluoromethyloxy, hydroxyC₁₋₄alkyloxy,
 C₁₋₄alkylsulfonyl, C₁₋₄alkyloxyC₁₋₄alkyloxy, C₁₋₄alkyloxycarbonyl,
 aminoC₁₋₄alkyloxy, di(C₁₋₄alkyl)aminoC₁₋₄alkyloxy, di(C₁₋₄alkyl)amino,
 35 di(C₁₋₄alkyl)aminocarbonyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl,
 di(C₁₋₄alkyl)aminoC₁₋₄alkylaminoC₁₋₄alkyl,
 di(C₁₋₄alkyl)amino(C₁₋₄alkyl)amino, di(C₁₋₄alkyl)amino(C₁₋₄alkyl)aminoC₁₋₄alkyl,
 di(C₁₋₄alkyl)aminoC₁₋₄alkyl(C₁₋₄alkyl)amino,

- di(C₁₋₄alkyl)aminoC₁₋₄alkyl(C₁₋₄alkyl)aminoC₁₋₄alkyl,
 aminosulfonylamino(C₁₋₄alkyl)amino,
 aminosulfonylamino(C₁₋₄alkyl)aminoC₁₋₄alkyl,
 di(C₁₋₄alkyl)aminosulfonylamino(C₁₋₄alkyl)amino,
 5 di(C₁₋₄alkyl)aminosulfonylamino(C₁₋₄alkyl)aminoC₁₋₆alkyl, cyano,
 piperidinylC₁₋₄alkyloxy, pyrrolidinylC₁₋₄alkyloxy, aminosulfonylpiperazinyl,
 aminosulfonylpiperazinylC₁₋₄alkyl, di(C₁₋₄alkyl)aminosulfonylpiperazinyl,
 di(C₁₋₄alkyl)aminosulfonylpiperazinylC₁₋₄alkyl, hydroxyC₁₋₄alkylpiperazinyl,
 hydroxyC₁₋₄alkylpiperazinylC₁₋₄alkyl, C₁₋₄alkyloxypiperidinyl,
 10 C₁₋₄alkyloxypiperidinylC₁₋₄alkyl, hydroxyC₁₋₄alkyloxyC₁₋₄alkylpiperazinyl,
 hydroxyC₁₋₄alkyloxyC₁₋₄alkylpiperazinylC₁₋₄alkyl,
 (hydroxyC₁₋₄alkyl)(C₁₋₄alkyl)amino, (hydroxyC₁₋₄alkyl)(C₁₋₄alkyl)aminoC₁₋₄alkyl,
 di(hydroxyC₁₋₄alkyl)amino, di(hydroxyC₁₋₄alkyl)aminoC₁₋₄alkyl, furanyl, furanyl
 substituted with -CH=CH-CH=CH-, pyrrolidinylC₁₋₄alkyl, pyrrolidinylC₁₋₄alkyloxy,
 15 morpholinyl, morpholinylC₁₋₄alkyloxy, morpholinylC₁₋₄alkyl,
 morpholinylC₁₋₄alkylamino, morpholinylC₁₋₄alkylaminoC₁₋₄alkyl, piperazinyl,
 C₁₋₄alkylpiperazinyl, C₁₋₄alkylpiperazinylC₁₋₄alkyloxy, piperazinylC₁₋₄alkyl,
 C₁₋₄alkylpiperazinylC₁₋₄alkyl, C₁₋₄alkylpiperazinylC₁₋₄alkylamino,
 C₁₋₄alkylpiperazinylC₁₋₄alkylaminoC₁₋₆alkyl, tetrahydropyrimidinylpiperazinyl,
 20 tetrahydropyrimidinylpiperazinylC₁₋₄alkyl, piperidinylaminoC₁₋₄alkylamino,
 piperidinylaminoC₁₋₄alkylaminoC₁₋₄alkyl,
 (C₁₋₄alkylpiperidinyl)(hydroxyC₁₋₄alkyl)aminoC₁₋₄alkylamino,
 (C₁₋₄alkylpiperidinyl)(hydroxyC₁₋₄alkyl)aminoC₁₋₄alkylaminoC₁₋₄alkyl,
 pyridinylC₁₋₄alkyloxy,
 25 hydroxyC₁₋₄alkylamino, hydroxyC₁₋₄alkylaminoC₁₋₄alkyl,
 di(C₁₋₄alkyl)aminoC₁₋₄alkylamino, aminothiadiazolyl,
 aminosulfonylpiperazinylC₁₋₄alkyloxy, or thiophenylC₁₋₄alkylamino;
 each R⁵ and R⁶ can be placed on the nitrogen in replacement of the hydrogen;
- 30 aryl in the above is phenyl, or phenyl substituted with one or more substituents each
 independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, trifluoromethyl, cyano or
 hydroxycarbonyl.

2. A compound as claimed in claim 1 wherein
 35 each Z is nitrogen;
 R¹ is -C(O)NR⁷R⁸, -C(O)-C₁₋₆alkanediylSR⁹, -NR¹⁰C(O)N(OH)R⁹,
 -NR¹⁰C(O)C₁₋₆alkanediylSR⁹, -NR¹⁰C(O)C=N(OH)R⁹ or another Zn-chelating-
 group

wherein R^7 and R^8 are each independently selected from hydrogen, hydroxy, hydroxyC₁₋₆alkyl, or aminoC₁₋₆alkyl;

R^2 is hydrogen, halo, hydroxy, amino, nitro, C₁₋₆alkyl, C₁₋₆alkyloxy, trifluoromethyl or di(C₁₋₆alkyl)amino;

5 R^3 is hydrogen, hydroxy, amino, hydroxyC₁₋₆alkyl, C₁₋₆alkyl, C₁₋₆alkyloxy, arylC₁₋₆alkyl, aminocarbonyl, aminoC₁₋₆alkyl, C₁₋₆alkylaminoC₁₋₆alkyl or di(C₁₋₆alkyl)aminoC₁₋₆alkyl;

R^4 is hydrogen;

10 $\text{---} \bigcirc \text{A}$ is a radical selected from (a-1), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (a-9), (a-10), (a-11), (a-12), (a-13), (a-14), (a-15), (a-16), (a-17), (a-18), (a-19), (a-20), (a-21), (a-22), (a-23), (a-24), (a-25), (a-26), (a-28), (a-29), (a-30), (a-31), (a-32), (a-33), (a-34), (a-35), (a-36), (a-37), (a-38), (a-39), (a-40), (a-41), (a-42), (a-44), (a-45), (a-46), (a-47), (a-48) or (a-51);

each s is independently 0, 1, 2, 3 or 4;

15 R^5 is hydrogen; halo; hydroxy; amino; nitro; trihaloC₁₋₆alkyl; trihaloC₁₋₆alkyloxy; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylsulfonyl; hydroxyC₁₋₆alkyl; aryloxy; di(C₁₋₆alkyl)amino; cyano; thiophenyl; furanyl; furanyl substituted with hydroxyC₁₋₆alkyl; benzofuranyl; imidazolyl; oxazolyl; oxazolyl substituted with aryl and C₁₋₆alkyl;

20 C₁₋₆alkyltriazolyl; tetrazolyl; pyrrolidinyl; pyrrolyl; morpholinyl; C₁₋₆alkylmorpholinyl; piperazinyl; C₁₋₆alkylpiperazinyl; hydroxyC₁₋₆alkylpiperazinyl; C₁₋₆alkyloxypiperidinyl; pyrazolyl; pyrazolyl substituted with one or two substituents selected from C₁₋₆alkyl or trihaloC₁₋₆alkyl; pyridinyl; pyridinyl substituted with C₁₋₆alkyloxy, aryloxy or aryl; pyrimidinyl;

25 quinolinyl; indole; phenyl; or phenyl substituted with one or two substituents independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy or trifluoromethyl; and

R^6 is hydrogen; halo; hydroxy; amino; nitro; trihaloC₁₋₆alkyl; trihaloC₁₋₆alkyloxy; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylsulfonyl; hydroxyC₁₋₆alkyl; aryloxy; di(C₁₋₆alkyl)amino; cyano; pyridinyl;

30 phenyl; or phenyl substituted with one or two substituents independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy or trifluoromethyl.

3. A compound as claimed in claim 1 wherein n is 1; each Q is $\text{---} \text{C} \begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$; R^1 is $\text{---} \text{C}(\text{O})\text{NR}^7\text{R}^8$, or $\text{---} \text{NHC}(\text{O})\text{C}_{1-6}\text{alkanediylSH}$ wherein R^7 and R^8 are each

35 independently selected from hydrogen, hydroxy or hydroxyC₁₋₆alkyl; R^2 is hydrogen or nitro; R^3 is hydrogen; when Z is equal to $\text{---} \text{CH} \begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$, then $\text{---} \text{L}$ is the bivalent radical

-C₁₋₆alkanediylNH-; R⁴ is hydrogen, C₁₋₆alkyl or aryl; $\text{---}\text{A}\cdot$ is a radical selected from (a-1) or (a-21); each s is independently 0, 1 or 2; and each R⁵ is independently selected from hydrogen; halo; trihaloC₁₋₆alkyl; trihaloC₁₋₆alkyloxy; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; aryloxy, cyano or phenyl.

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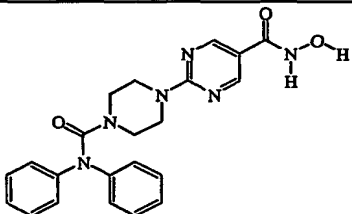
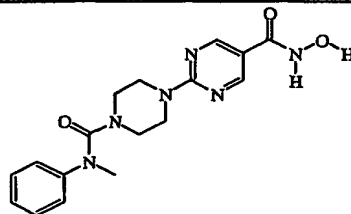
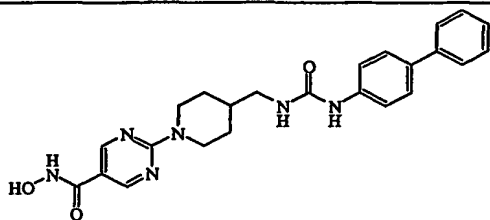
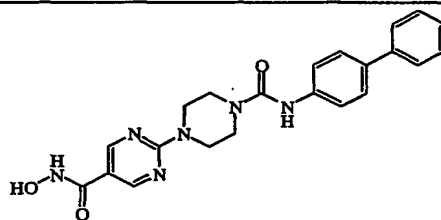
4. A compound as claimed in claim 1 and 3 wherein n is 1; each Q is $\text{---}\text{C}\equiv$; each X is nitrogen; each Y is nitrogen; R¹ is -C(O)NH(OH); R² is hydrogen; R³ is hydrogen; when Z is equal to $\text{---}\text{CH}\cdot$, then -L- is the bivalent radical

-C₁₋₆alkanediylNH-; R⁴ is hydrogen, C₁₋₆alkyl or aryl; $\text{---}\text{A}\cdot$ is the radical (a-1); each s is independently 0 or 1; and each R⁵ is independently selected from hydrogen or phenyl.

10

5. A compound according to claim 1, 3 and 4 selected from compounds No. 4, No. 48, No. 5 and No. 6.

15

	
Co. No. 4	Co. No. 48
	
Co. No. 5	Co. No. 6

6. A pharmaceutical composition comprising pharmaceutically acceptable carriers and as an active ingredient a therapeutically effective amount of a compound as claimed in claim 1 to 5.

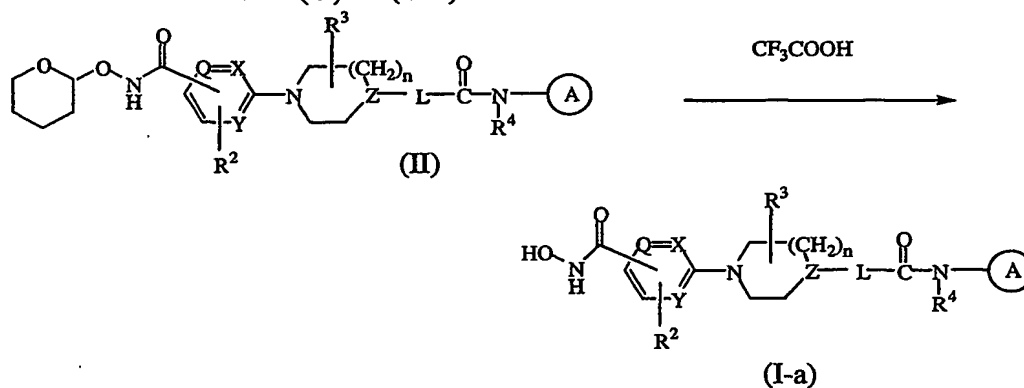
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7. A process of preparing a pharmaceutical composition as claimed in claim 6 wherein the pharmaceutically acceptable carriers and a compound as claimed in claim 1 to 5 are intimately mixed.

8. A compound as claimed in any of claims 1 to 5 for use as a medicine.
9. Use of a compound as claimed in any of claims 1 to 5 for the manufacture of a medicament for the treatment of proliferative diseases.

5

10. A process for preparing a compound as claimed in claim 1, characterized by reacting an intermediate of formula (II) with an appropriate acid, such as for example, trifluoro acetic acid, yielding a hydroxamic acid of formula (I-a), wherein R¹ is -C(O)NH(OH).



10

11. A method of detecting or identifying a HDAC in a biological sample comprising detecting or measuring the formation of a complex between a labelled compound as defined in claim (I) and a HDAC.

15

12. A combination of an anti-cancer agents and a HDAC inhibitor as claimed in any of claims 1 to 5.